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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	09/674,607	PRASHAR ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,34 and 37-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21, 34, and 37-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This action is in response to the amendment filed January 3, 2005. Claims 21, 34 and 37-46 are pending.

Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. Applicant's election of Group VI in the response of January 5, 2004 and of the species of the disease glomerulonephritis, the cell of peripheral T lymphocytes and the expression profile comprising each of SEQ ID NO: 1-34 in the response of April 21, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 34 and 37-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods for diagnosing a disorder in a subject wherein the methods comprise providing a gene expression profile of at least 5 genes from a T-lymphocyte population from a subject and comparing this gene expression profile to a second T lymphocyte gene expression profile from a subject having a disorder and to a third gene expression profile from a normal T-lymphocyte population and determining if the subject has the disorder. In particular, the disorder is the inflammatory disease glomerulonephritis, the T lymphocyte population comprises peripheral T lymphocytes and the expression profile comprises SEQ ID NO: 1-34.

The specification exemplifies methods of generating expression profiles from T lymphocyte cells and methods of comparing gene expression profiles from treated and untreated populations of T lymphocytes. The specification (see Example 5 and Figure 4) teaches 16 sequences that are up-regulated or down-regulated in activated Jurkat cells as compared to quiescent Jurkat cells. In Figure 5, SEQ ID NO:14-33 are disclosed as being differentially expressed in activated versus quiescent T lymphocytes. The specification outlines the steps that one could perform to compare the gene expression patterns of T lymphocytes MPCs from undiagnosed patients to the gene expression patterns of normal T lymphocytes and T lymphocytes obtained from subjects having a disorder such as glomerulonephritis (pages 47-48). It is stated that "(t)he expression profile prepared from the subject can then be compared to the expression profiles prepared from T lymphocytes isolated from patients with various inflammatory disorders...to determine which expression profile most closely matches the expression

profile prepared from the patient, thereby, diagnosing whether the patient has a sterile inflammatory disease, immunodeficiency disorder or autoimmune disorder."

However, the specification has not provided sufficient guidance to enable the skilled artisan to diagnose a disorder by comparing the expression pattern of T lymphocytes from a subject to the expression profile of T lymphocytes from reference normal or glomerulonephritis disease states or from other disease states. The specification does not provide any specific gene profiles that conclusively represent a normal or glomerulonephritis or other type of disease state. The claims as broadly written encompass analyzing the expression profile of any gene or combination of genes. Thereby, the claims encompass analyzing a significantly large number of nucleic acids to determine which of the nucleic acids have an expression pattern specifically correlated with glomerulonephritis or another type of disease. Even if the claims were amended to reflect the elected invention of the combination of sequences of SEQ ID NO: 1-34, the specification has not establish that any one of these sequences or combinations of sequences is associated with a particular disease state. While the specification has shown that the expression of fragments of nucleic acid vary in activated and quiescent T lymphocytes, the specification has not establish that the expression pattern of the nucleic acid fragments vary between normal and disease states. Accordingly, to practice the claimed invention, one must first determine an expression profile that is generally characteristic of a normal T lymphocyte (specifically a peripheral T lymphocyte) and an expression profile that is specifically characteristic of T lymphocytes from individual's having sterile inflammatory disorders, autoimmune

disorders, immunodeficiency disorders, cancer and/or GVHD (specifically the disorder glomerulonephritis). Such experimentation is considered undue. While the techniques for creating gene expression profiles are known in the art, the results of performing such methods as they relate to normal and diseased T lymphocytes are not known and are unpredictable. Specifically, it is unpredictable as to what would constitute a normal T lymphocyte gene expression profile and what would constitute a T lymphocyte gene expression profile characteristic of sterile inflammatory disorders, autoimmune disorders, immunodeficiency disorders, cancer or GVHD, or characteristic of glomerulonephritis. The specification does not provide any working examples of diagnosing a disease state by comparing the T lymphocyte gene expression profile of a patient to that of a reference normal or disease state. Extensive experimentation would be required to obtain gene expression profiles that specifically represent the normal state of T lymphocytes and disease state of T lymphocytes and which could be used to diagnose a disease state in the general population. Additionally, the specification does not provide sufficient guidance as to how to evaluate the results of the comparison step and as to how to determine whether a gene profile "most closely matches" a disease or control state in order to allow for a diagnosis of a disease state. The specification does not teach any particular genes that are up-regulated or down-regulated in T lymphocytes from patients having a disorder as compared to T lymphocytes from normal subjects. There are also no teachings in the specification as to the number of genes that must be commonly up-regulated or down-regulated in order to diagnose a disease state. Similarly, the specification does not teach if any particular class or

member of a class of genes must be analyzed to allow for the diagnosis of a disease state. Of the sequences set forth in Figures 4 and 5, 21 appear to be of unknown function (i.e. do not "match" any known human gene sequence). Additionally, these sequences appear to represent small fragments of gene sequences. There are no teachings in the specification as to whether the gene fragments are specific for a single gene or cross hybridize with additional genes, that may or may not be expressed in T lymphocytes from different disease states. It is unclear as to which of the sequences disclosed in the specification are up-regulated or down-regulated in sterile inflammatory disorders, autoimmune disorders, immunodeficiency disorders, cancer or GVHD, or and which of the sequences could be used to diagnose a disease state such as glomerulonephritis.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art of identifying specific

gene expression patterns associated with particular disease states is highly unpredictable. There is no predictable means for determining which nucleic acids combination of nucleic acids are specifically up-regulated or down-regulated in diseased versus normal cells. Such information can only be obtained through extensive experimentation. Additionally, the specification does not provide sufficient guidance as to how to interpret the results of methods which compare gene expression profiles and does not adequately teach how one determines if a gene expression profile is sufficiently similar so as to allow for the diagnosis of a disease. Further, the specification does not teach the "novel aspects of the invention." That is, the specification does not teach any particular genes or gene expression profiles that are characteristic of normal or diseased T lymphocytes. The specification does not provide any reasonable expectation that one could obtain a gene expression profile specific for glomerulonopephritis or other disorder without undue experimentation. Accordingly, in view of the lack of specific guidance and disclosure provided in the specification, undue experimentation would be required to practice the claimed invention.

Response to Arguments:

In the response filed January 3, 2005, Applicants traverse this rejection by arguing that the specification is enabling for the full scope of the claims. It is asserted that the specification discloses genes, such as those listed in Figures 4 and 5 which are activated by antigens, pathogens or other inflammatory mediators and that similar expression profiles can be obtained from subjects to be diagnosed. Applicants argue that the genes of Figures 4 and 5 are either up-regulated or down-regulated and thereby

can be compared to a patient's gene expression profile to diagnose a disease. Applicants further argue that to practice the claimed invention does not require knowledge of all the genes that are up-regulated or down-regulated in a disease. Applicants also assert that all that is needed to make and compare a gene expression profile are the T-cell samples and the teachings of the instant specification.

Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. While Applicants assert that they teach more than 30 genes that can serve as markers for diseases, Applicants have not in fact taught any genes that are specifically associated with the occurrence of glomerulonopephritis or other sterile inflammatory disease, immunodeficiency disorder, autoimmune disorder, cancer or GVHD. Rather, the specification (see Example 5 and Figure 4) teaches 16 sequences that are up-regulated or down-regulated in activated Jurkat cells as compared to quiescent Jurkat cells. In Figure 5, SEQ ID NO:14-33 are disclosed as being differentially expressed in activated versus quiescent T lymphocytes. The finding that these genes are up-regulated or down-regulated in quiescent or activated cells in culture is clearly distinct form establishing that these genes are up-regulated or down-regulated in glomerulonopephritis or other specific disorders. Applicants do not provide any scientific evidence or argument to support a conclusion that the results obtained with activated and quiescent tissue culture cells would be expected to be equivalent to the results obtained in vivo in patients having glomerulonopephritis or other sterile inflammatory disease, immunodeficiency disorder, autoimmune disorder, cancer or GVHD. Additionally, the specification has not

adequately taught the skilled artisan how to use the sequences set forth in Figures 4 and 5 to detect the expression of specific genes. Of the sequences set forth in Figures 4 and 5, 21 appear to be of unknown function (i.e. do not "match" any known human gene sequence). These sequences also appear to represent small fragments of gene sequences, rather than full length gene sequences. There are no teachings in the specification as to whether the gene fragments are specific for a single gene or cross hybridize with additional genes. Thereby, undue experimentation would be required to use the disclosed sequences because this would first require determining which, if any, of these gene sequences/fragments specifically hybridizes to a particular T-lymphocyte mRNA. Following such a determination, one would then have to determine which of the combinations of genes is specifically up-regulated or down-regulated in glomerulonopephritis or other disorders in order to arrive at a method which can be used for diagnostic purposes. Such random, trial-by-error experimentation is considered to be undue.

Applicants argue that not all genes up-regulated or down-regulated in a disease need to be identified in order to practice the claimed invention. However, the claims do in fact require the analysis of combinations of genes including 5, 10, 50, 100, 500 and 1000 genes. In order to interpret the results of such a comparison, one would need to know the identity of the genes that are being analyzed. However, the specification does not teach any sets of, e.g., of 5 or 10 or 50 or 100 or 1000 specific genes, which are expressed in T cells and whose expression is diagnostic of glomerulonopephritis or other disorders.

Applicants arguments seem to predicated on the fact that they have identified genes that are up-regulated or down-regulated in tissue culture cells and from this information, the skilled artisan can select which, if any, of these genes and which of all other possible genes are associated with a particular disease in order to arrive at methods for diagnosing a disease. While methods may be known in the art for generating a gene expression profile and for searching for genes, such teachings provide only the guidelines that enable practioners to perform experiments to try to generate gene expression profiles characteristic of particular disease. Such teachings are not equivalent to providing specific genes and combinations of genes that are up-regulated or down-regulated in glomerulonopephritis or other disorders. Further, the present claims are not drawn to methods of searching for a gene that is expressed in a subject or general methods of performing differential display. Rather, the present claims are limited to methods for diagnosing of sterile inflammatory disease, immunodeficiency disorder, autoimmune disorder, cancer or GVHD, and particularly diagnosing glomerulonopephritis.

It is maintained that the novel aspect of the claims is the combination of genes whose expression is to be analyzed as indicative of glomerulonopephritis. The novel aspects of the invention are not the process steps of creating a gene expression profile. Such methodology is well known in the art, as clearly indicated by Applicants teachings at page 14 of the specification that "Gene expression profiles can be produced by any means known in the art" and the listing of 10 representative publications teaching methods for generating a gene expression profile.

Applicants have argued that the claimed methods are fully enabled by the specification because the specification teaches how to compare gene expression profiles and how to diagnose a subject based on similar gene expression profiles. However, the specification does not sufficiently characterize the identity of the genes present in the gene expression profile and does not provide sufficient guidance to enable the skilled artisan to diagnose a disease based on a finding of similar expression profiles. The specification does not teach what would constitute a "similar" gene expression profile. For example, for profiles containing 1000 genes, would each of the 1000 genes up-regulated or down-regulated in the reference disease profile also need to be up-regulated or down-regulated in the subject's profile in order for one to arrive at a conclusion that the profiles are similar? If not, how many of the genes would need to show identical changes in expression in order for two profiles to be considered to be "similar"? What would be the identity of the 1000 genes? Do all 1000 genes need to be up-regulated or down-regulated in the disease? If not, of the 1000 genes, how many of these genes need to actually be informative in order to allow for the diagnosis of a disease? Would this finding be different based on the particular gene or combination of genes that are to be analyzed? For instance, if one gene is found to be up-regulated in glomerulonephritis and in periodontal disease, would a gene expression profile showing the up-regulation of this one gene be sufficient to allow for the diagnosis of glomerulonephritis? Since the claims are not limited to the analysis of any particular class of genes (e.g., tumor suppressor gene expression as diagnostic of cancer), It would be expected that for many genes, a single gene alone or in fact a combination of

5 genes would not be diagnostic of a disease. However, there are no teachings in the specification as to which particular combinations of genes are associated with glomerulonopephritis or other sterile inflammatory disease, immunodeficiency disorder, autoimmune disorder, cancer or GVHD. There are also no teachings in the specification as to the particular number of genes that must be up-regulated or down-regulated in order to allow for a reasonable diagnosis of glomerulonopephritis or other disorder. Accordingly, Applicants have not adequately taught the skilled artisan how to determine whether a subject's gene expression profile comprising SEQ ID NO: 1-34 or comprising any genes of any identity is sufficiently similar to a reference disease gene profile in order to allow the artisan to conclude that the subject has glomerulonopephritis or another sterile inflammatory disease, immunodeficiency disorder, autoimmune disorder, cancer or GVHD.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 34 and 37-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 34 and 37-46 are indefinite. The claims are drawn to methods for diagnosing a disease and include the step of comparing an expression profile from a subject to an expression profile from a T lymphocyte population from a subject having a disease and to an expression profile from a normal T lymphocyte population. Following the comparing step, the claim includes a limitation of determining if the subject has a

sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD. However, the claim does not clearly set forth the relationship between the comparing and determining step and does not clearly indicate how the comparison step results in the determination of whether the subject has a sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD.

Response to Arguments:

In the response filed January 3, 2005, Applicants traverse this rejection by stating that the claims have been amended and now indicate that if the first gene expression profile is similar to the gene expression profile of a patient having one of the stated diseases as compared to a normal profile, then a correct diagnosis can be made.

This argument has been fully considered but is not persuasive because the claims as amended do not set forth this concept. Rather, the claims recite only that the gene expression profile from a subject is compared to a second and third gene expression profile, "thereby determining if the subject has a sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD." The claims do not require an analysis of the expression profiles such that one would arrive at a conclusion that the subject's gene expression profile is in some unstated manner "similar" to the gene expression representative of a disease and not "similar" to a normal profile. It is maintained that the claims do not clarify how the step of comparing results in such a determination and the claims do not clearly set forth how the step of comparing results in the diagnosis of sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD. Further, if the claims did recite that the

analysis required identifying similar profiles, it would remain unclear as to what was intended to be encompassed by a similar profile. For example, would the presence of one out of 5 genes present in the disease reference profile constitute a similar profile? Or would a similar profile require equivalent levels of expression of each of or a particular percentage of the genes expressed in the second gene expression profile?

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
March 16, 2005

CARLA J. MYERS
PRIMARY EXAMINER